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CD40.SARS-COV2 VACCINE, BUT NOT mRNA, INDUCES SPECIFIC CD8+ T MEMORY STEM CELLS

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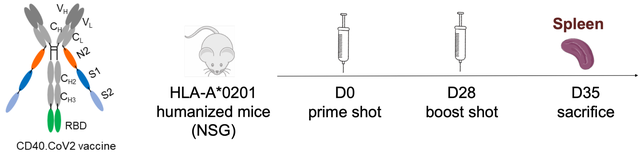
BACKGROUND

Vaccination plays a major role in controlling SARS-CoV-2 infection but faces the issue of short-term protection. Beyond the generation of Abs, induction of memory CD8⁺T cells with stem cell-like (Tscm) properties is essential for long-term immunity to viruses. We have designed a sub-unit CD40.CoV2 vaccine which targets Spike (S) and nucleocapsid (N) regions from SARS-CoV2 to antigen presenting cells with comparable immunogenicity and protective effect than mRNA BNT162b2 (Pfizer-BioNTech) in preclinical models (Coléon S. EBioMed 2022). We hypothesized that CD40.CoV2 vaccine will elicit CD8⁺ Tscm cells.

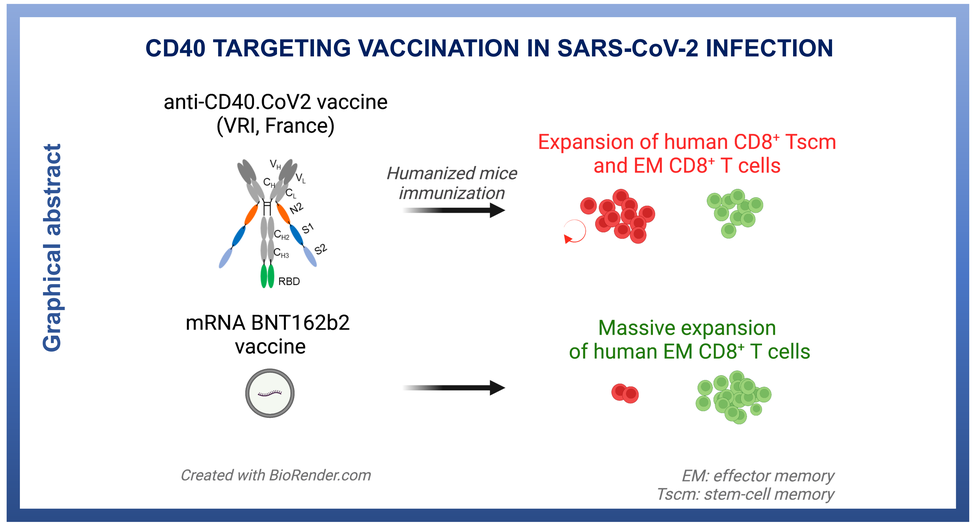
METHODS

CD40.CoV2 vaccine is a fully humanized mAb fused to RBD (aa 318-541) and N (aa 276-411). Humanized (hu) NSG mice (HIS-mice) (n=6/group) received: i) CD40.CoV2 (10µg equal to 1.3µg of RBD, i.p.) +/- poly-ICLC (TLR3 agonist; 50µg, provided by Oncovir), or ii) mRNA BNT162b2 (1µg, i.m. Pfizer-BioNTech), or iii) IgG4.CoV2 (10µg, i.p.) as non-CD40-targeting control. Phenotype and function of splenic S and N-specific T cells were assessed at W5.



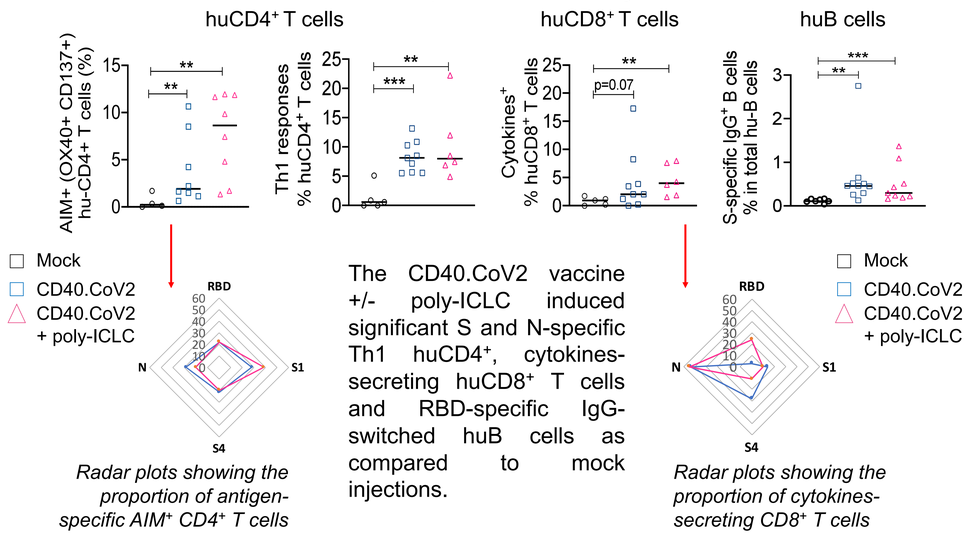
We monitored by flow cytometry:

- the total specific-huT cells using AIM and ICS *in vitro* assays with S-, N-overlapping peptide pools (OLPs) and huB-cell responses using a biotinylated Spike,
- the *ex vivo* frequency of huCD8+ Tscm (CD3⁺ CD8⁺ CD95⁺ CD45RA⁺ CD62L⁺), T_{CM} (central memory, CD3⁺ CD8⁺ CD45RA⁻ CD62L⁺) and T_{EM} (effector memory, CD3⁺ CD8⁺ CD45RA⁻ CD62L⁻) cells,
- the proliferative capacities of huCD8⁺ Tscm, T_{CM}, and T_{EM} cells as well as their abilities to produce cytokines after an *in vitro* re-stimulation with RBD and N OLPs.



RESULTS

1. We first monitored T and B-cell responses elicited by the CD40.CoV2 vaccine

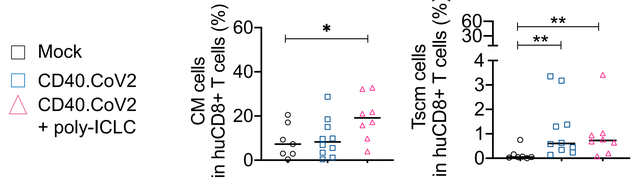


The CD40.CoV2 vaccine +/- poly-ICLC induced significant S and N-specific Th1 huCD4⁺, cytokines-secreting huCD8⁺ T cells and RBD-specific IgG-switched huB cells as compared to mock injections.

Radar plots showing the proportion of antigen-specific AIM⁺ CD4⁺ T cells

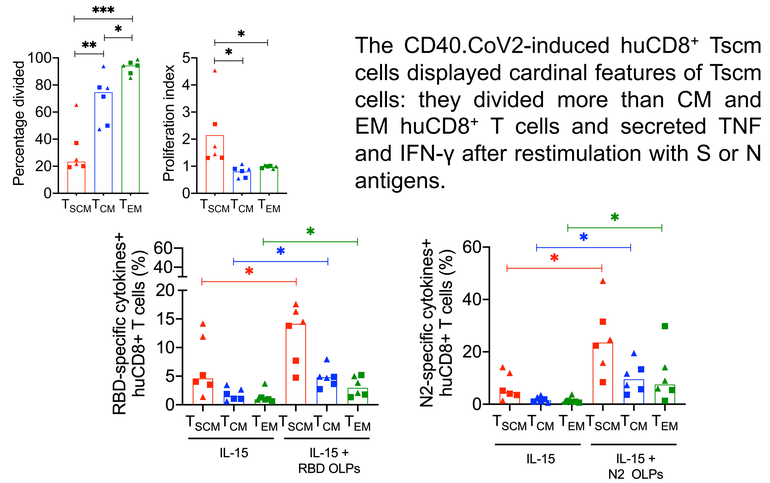
Radar plots showing the proportion of cytokines-secreting CD8⁺ T cells

2. We further looked at the memory CD4⁺ and CD8⁺ huT cell expanded by the CD40.CoV2 vaccine



We observed a significant increased of huCD8⁺ memory CM and Tscm cells in the vaccinees compared to mock animals.

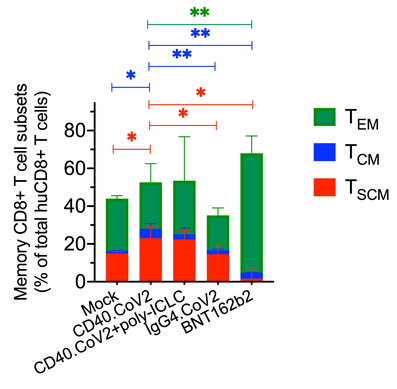
3. We then compared the functionalities of huCD8⁺ Tscm, CM, and effector memory (EM) cells elicited by the CD40.CoV2 vaccine used with (triangle) or without (rectangle) adjuvant



The CD40.CoV2-induced huCD8⁺ Tscm cells displayed cardinal features of Tscm cells: they divided more than CM and EM huCD8⁺ T cells and secreted TNF and IFN-γ after restimulation with S or N antigens.

4. We finally compared the induction of CD8⁺ Tscm, CM and EM between the CD40.Cov2, mRNA BNT162b2 or IgG4.CoV2 non-targeting vaccination

CD40.CoV-2 vaccine +/- adjuvant induced higher frequencies of huCD8 Tscm cells and CD8⁺ T_{CM} cells. In contrast, BNT162b2 induced predominantly CD8⁺ T_{EM} cells but not Tscm cells.



CONCLUSION

The CD40.SARS.CoV2, but not BNT162b2 vaccine, stimulates selective enrichment in S- and N-specific CD8⁺ Tscm cells that support long-lasting anti-viral immunity. CD40.CoV2 sub-unit is under clinical development as a booster vaccine aimed to maintain durable anti-viral T and humoral responses.

Financial supports:
ANR-20-COV6-0004 & Labex VRI ANR-10-LABX-77-01
Laury Nguema is receiving a PhD scholarship from UPEC University, France